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(71) Applicant *(for all designated States except US)*: PHARNO-WEDROPHARM GMBH [DE/DE]; Neue Straße 6, Postfach 13 51, D-2110 Buchholz/Nordheide (DE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)* : DUMONT, Raymond [CH/CH]; Abendstraße 1, CH-3027 Bern (CH).

(74) Agents: SCHUPFNER, Gerhard, D. et al.; Müller, Schupfner & Gauger, Karlstraße 5, D-2110 Buchholz/Nordheide (DE).

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(54) Title: AROMATIC SULFONAMIDE DERIVATIVES, THEIR USE AS ENZYME INHIBITORS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract

Aromatic sulfonamide derivatives, particularly benzene-sulfonamide, 4-fluorobenzenesulfonamide, 5-chloro-1-naphthalenesulfonamide and 5-isoquinolinesulfonamide derivatives are provided that inhibit Ca^{2+}-dependent enzymes and proteins such as Phospholipase A_2, protein kinases such as Protein Kinase C, and inhibit membrane fusion, thereby being a valuable drug for the treatment of inflammation, arthritis, infarction, nephritis and many other types of tissue injury.

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Aromatic sulfonamide derivatives, their use as enzyme inhibitors and pharmaceutical compositions containing them.

This invention relates to aromatic sulfonamide derivatives, especially to benzenesulfonamide-, 4-fluorobenzenesulfonamide-, 5-chloro-1-naphthalenesulfonamide- and 5-isoquinolinesulfonamide derivatives.

This invention particularly relates to aromatic sulfonamide derivatives that inhibit Ca^{2+} -dependent enzymes and proteins such as Phospholipase A_2 , protein kinases such as Protein Kinase C, and membrane fusion, thereby being a valuable drug for the treatment of inflammation, arthritis, infarction, nephritis and many other types of tissue injury, and provides a process for the preparation thereof.

The invention further relates to pharmaceutical compositions containing these derivatives.

The invention is defined in detail in the claims.

A groups in formula I-IV particularly include L-phenylalanine, L-alanine, L-proline, L-valine, L-tryptophane and L-tyrosine - where the N atom is bound to the SO_2 group.

When the R_1 group in formula I-IV is hydrogen, then the R_2 group is benzyl, biphenyl or a C_3 or C_6 alkylene chain. A 6 membered heterocyclic ring (piperazine) may be formed through an ethylene group and adjacent nitrogen atoms.

Exemplary benzenesulfonamide derivatives of the invention include:

(1) N-benzenesulfonyl-L-phenylalanine piperazineamide [referred to as compound 1];

(2) N-benzenesulfonyl-L-alanine piperazineamide [referred to as compound 2];

(3) N-benzenesulfonyl-L-valine piperazineamide [referred to as compound 3];

(4) N-benzenesulfonyl-L-proline piperazineamide [referred to as compound 4];

(5) N-benzenesulfonyl-L-phenylalanine-1,6-diaminohexaneamide [referred to as compound 5];

(6) N-benzenesulfonyl-L-phenylalanine-1,3-diaminopropaneamide [referred to as compound 6];

(7) N-benzenesulfonyl-L-phenylalanine biphenylamide [referred to as compound 7];

(8) N-benzenesulfonyl-L-alanine biphenylamide [referred to as compound 8];

(9) N-benzenesulfonyl-L-valine biphenylamide [referred to as compound 9];

(10) N-benzenesulfonyl-L-proline biphenylamide [referred to as compound 10];

(11) N-benzenesulfonyl-L-tryptophane biphenylamide [referred to as compound 11];

(12) N-benzenesulfonyl-L-tyrosine biphenylamide [referred to as compound 12];

Exemplary 4-fluorobenzenesulfonylamide derivatives of the invention include:

(13) N-(4-fluorobenzenesulfonyl)-L-phenylalanine piperazineamide [referred to as compound 13];

(14) N-(4-fluorobenzenesulfonyl)-L-alanine piperazineamide [referred to as compound 14];

(15) N-(4-fluorobenzenesulfonyl)-L-valine piperazineamide [referred to as compound 15];

(16) N-(4-fluorobenzenesulfonyl)-L-proline piperazineamide [referred to as compound 16];

(17) N-(4-fluorobenzenesulfonyl)-L-phenylalanine biphenylamide [referred to as compound 17];

(18) N-(4-fluorobenzenesulfonyl)-L-alanine biphenylamide [referred to as compound 18];

(19) N-(4-fluorobenzenesulfonyl)-L-valine biphenylamide [referred to as compound 19];

(20) N-(4-fluorobenzenesulfonyl)-L-proline biphenylamide [referred to as compound 20];

Exemplary 5-chloro-1-naphthalenesulfonamide derivatives of the invention include:

(21) N-(5-chloro-1-naphthalenesulfonyl)-L-phenylalanine piperazineamide [referred to as compound 21];

(22) N-(5-chloro-1-naphthalenesulfonyl)-L-valine piperazineamide [referred to as compound 22];

(23) N-(5-chloro-1-naphthalenesulfonyl)-L-proline piperazineamide [referred to as compound 23];

(24) N-(5-chloro-1-naphthalenesulfonyl)-L-alanine piperazineamide [referred to as compound 24];

(25) N-(5-chloro-1-naphthalenesulfonyl)-L-phenylalanine-1,6-diaminohexaneamide [referred to as compound 25];

(26) N-(5-chloro-1-naphthalenesulfonyl)-L-phenylalanine biphenylamide [referred to as compound 26];

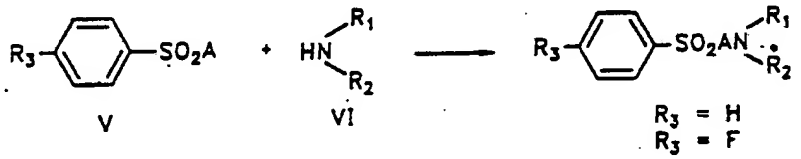
(27) N-(5-chloro-1-naphthalenesulfonyl)-L-alanine biphenylamide [referred to as compound 27];

(28) N-(5-chloro-1-naphthalenesulfonyl)-L-valine biphenylamide [referred to as compound 28];

(29) N-(5-chloro-1-naphthalenesulfonyl)-L-proline biphenylamide [referred to as compound 29];

(30) N-biphenyl-5-chloro-1-naphthalenesulfonamide [referred to as compound 30];

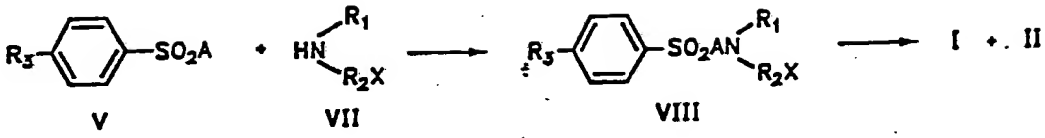
Exemplary 5-isoquinolinesulfonylamide derivatives of the invention include:
(31) N-(5-isoquinolinesulfonyl)-L-phenylalanine piperazineamide [referred to as compound 31];
(32) N-(5-isoquinolinesulfonyl)-L-valine piperazineamide [referred to as compound 32];
(33) N-(5-isoquinolinesulfonyl)-L-proline piperazineamide [referred to as compound 33];
(34) N-(5-isoquinolinesulfonyl)-L-alanine piperazineamide [referred to as compound 34];
(35) N-(5-isoquinolinesulfonyl)-L-phenylalanine-1,6-diaminohexaneamide [referred to as compound 35];
(36) N-(5-isoquinolinesulfonyl)-L-phenylalanine biphenylamide [referred to as compound 36];
(37) N-(5-isoquinolinesulfonyl)-L-valine biphenylamide [referred to as compound 37];
(38) N-(5-isoquinolinesulfonyl)-L-proline biphenylamide [referred to as compound 38];
(39) N-(5-isoquinolinesulfonyl)-L-alanine biphenylamide [referred to as compound 39];
(40) N-(5-isoquinolinesulfonyl)-D-proline biphenylamide [referred to as compound 40];
(41) N-biphenyl-5-isoquinolinesulfonamide [referred to as compound 41];
(42) N-benzyl-5-isoquinolinesulfonamide [referred to as compound 42];
The acid addition salts of the derivatives 1-6, 13-16, 21-25 and 31-35 according to this invention are pharmaceutically acceptable non-toxic salts and can be prepared by conventional methods. Suitable examples of such pharmaceutically acceptable acid addition salts include the salts of inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid and sulfuric acid; and the salts of organic acids such as acetic acid, citric acid, tartaric acid, lactic acid, succinic acid, fumaric acid, maleic acid, methanesulfonic acid and p-toluenesulfonic acid.
The benzenesulfonamide - and the 4-fluorobenzenesulfonamide derivatives of formula I-II can be prepared in accordance with the following equations:



V VI

wherein A is a part of an amino acid, R_1 is a hydrogen atom, R_2 is a biphenyl group and R_3 is a hydrogen or a fluor atom;

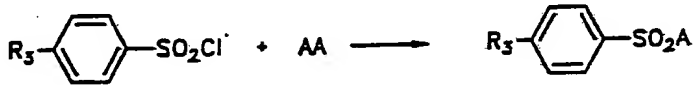
or



V VII VIII

wherein A is a part of an amino acid, R_1 is a hydrogen atom and R_2 a C_3 or C_6 alkylene chain; or R_1 and R_2 are linked directly to form a piperazine ring. R_3 is a hydrogen or a fluor atom and X a protective group.

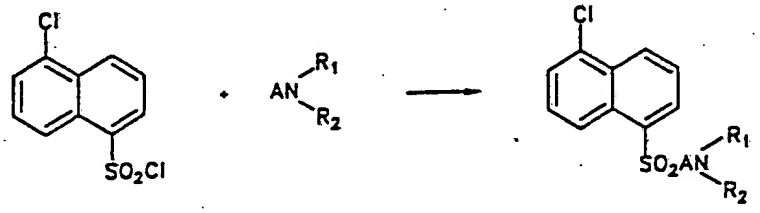
Derivative V can be prepared as follows:



IX V

wherein AA is an amino acid and R_3 is a hydrogen or a fluor atom.

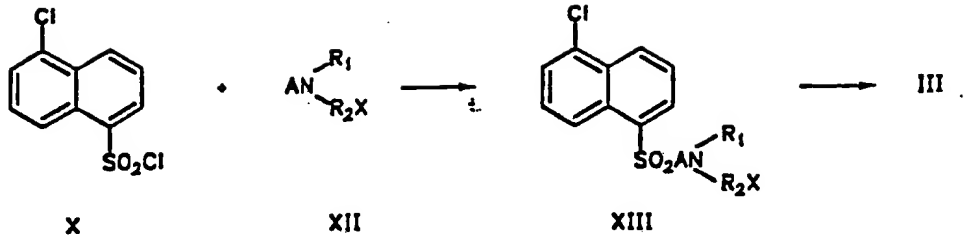
The naphthalenesulfonylamide derivatives of formula III can be prepared in accordance to the following equations:



X XI III

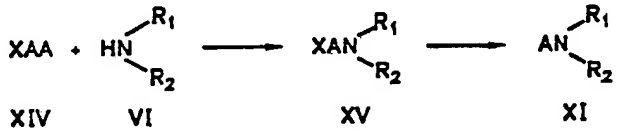
wherein A is a part of an amino acid or a single bond, R_1 is a hydrogen atom and R_2 is a biphenyl group;

or



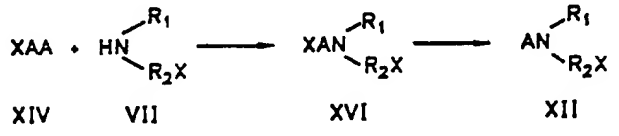
X XII XIII

wherein A is a part of an amino acid, R_1 is a hydrogen atom and R_2 a C_6 alkylene chain; or R_1 and R_2 are linked directly to form a piperazine ring. X is a protective group.
Derivative XI can be prepared as follows:



XIV VI XV XI

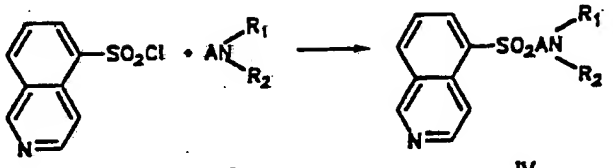
wherein AA is an amino acid, R_1 is a hydrogen atom, R_2 a biphenyl group and X a protective group.
Derivative XII can be prepared as follows:



XIV VII XVI XII

wherein AA is an amino acid, R_1 is a hydrogen atom and R_2 a C_6 alkylene chain; or R_1 and R_2 are linked directly to form a piperazine ring. X are protective groups.

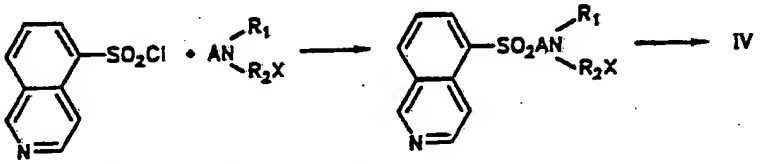
The isoquinolinesulfonamide derivatives of formula IV can be prepared in accordance to the following equations:



XVII XI IV

wherein A is a part of an amino acid or a single bond, R_1 is a hydrogen atom and R_2 a phenyl- or biphenyl group;

or



XVII XII XVIII

CBZ= carboxybenzyl
BOC= t-butoxycarbonyl

wherein A is a part of an amino acid, R_1 is a hydrogen atom and R_2 a alkylene chain; or R_1 and R_2 are linked directly to form a piperazine ring. X is a protective group.

Exemplary compounds of formula V include N-benzenesulfonyl-L-phenylalanine, N-benzenesulfonyl-L-alanine, N-benzenesulfonyl-L-valine, N-benzenesulfonyl-L-proline, N-benzenesulfonyl-L-tryptophane and N-benzenesulfonyl-L-tyrosine; N-(4-fluorobenzenesulfonyl)-L-phenylalanine, N-(4-fluorobenzenesulfonyl)-L-alanine, N-(4-fluorobenzenesulfonyl)-L-valine, N-(4-fluorobenzenesulfonyl)-L-proline.

Exemplary compounds of formula VI include 4-aminobiphenyl and 4-aminobenzyl.

Exemplary compounds of formula VII include N-CBZ-piperazine, N-BOC-1,6-diaminohexane and N-CBZ-1,3-diaminopropane.

Exemplary compounds of formula XI include L-phenylalanine biphenylamide, L-alanine biphenylamide, L-valin biphenylamide, L-prolin biphenylamide and D-proline biphenylamide.

Exemplary compounds of formula XII include L-phenylalanine-N-CBZ-piperazineamide, L-alanine-N-CBZ-piperazineamide, L-valine-N-CBZ-piperazineamide and L-phenylalanine-N-BOC-1,6-diaminohexaneamide.

The reaction between the compound of formula V and the compound of formula VI, respectively VII is best carried out in presence of dicyclohexylcarbodiimide (DCC) and a reaction medium like dimethylformamide (DMF) or dioxane; 1-hydroxy-benzotriazole is used to avoid racemization.

The amount of the compound of formula V preferably is the same as of the compound of formula VI or VII.

The amount of DCC is preferably about 1 to 5 equivalents and more preferably 1 to about 2 equivalents for each mol of the compound of formula V.

The amount of 1-hydroxybenzotriazole is preferably about 1 to 5 equivalents and more preferably 1 to about 2 equivalents for each mol of the compound of formula V.

The reaction between the compound of formula V and VI respectively VII can be carried out typically at a temperature of about -10°C to about 60°C and preferably from about 0°C to 30°C.

The reaction time which can be employed is typically about 1h to about 24h and preferably from 1h to about 5h.

The method of obtaining the compounds of formula I and II from VIII may vary depending upon the protective group of X selected, generally known methods can be employed in this invention.

For example when the protective group of X is an alkyloxycarbonyl group such as t-butoxycarbonyl, the desired products can be obtained by hydrolysis with an acid. When the protective group of X is an arylmethyloxycarbonyl group such as benzyloxycarbonyl, the desired compounds can be obtained by hydrogenation or hydrolysis with an acid.

The reaction between the compound of formula X and XI respectively XII is best carried out in presence of an acid acceptor. Exemplary acid acceptors which can be employed include alkali metal compounds such as hydroxide, bicarbonate or carbonate, e.g. sodium hydroxide, potassium hydroxide, sodium bicarbonate, sodium carbonate, potassiumcarbonate and tertiary amines such as triethylamine and pyridine.

In general the reaction is carried out in presence of a reaction medium. Exemplary reaction media which can be employed include ethers, such as dioxane or THF and halogenated hydrocarbons such as $CHCl_3$ and CH_2Cl_2.

The amount of the compound of formula X preferably is the same as of the compounds of formula XI or XII.

The amount of the acid acceptor employed is preferably about 2 to 5 equivalents and more preferably about 2 to 3 equivalents for each mol of the compound of formula X.

The reaction between the compound of formula X and XI respectively XII can be carried out typically at a temperature of about 10°C to about 60°C and preferably at 20°C to 30°C.

The reaction time which can be employed is typically about 1h to about 24h and preferably from 1h to about 5h.

The method of obtaining the compound of formula III from XIII can be carried out under the same conditions as the reaction from the compound of formula VIII to the compound of formula I and II.

The reaction between the compound of formula XVII and XI respectively XII can be carried out under the same condition as the reaction between the compound of formula X and XI respectively

XII except that the amount of the compound of formula XVII preferably is 0.9 equivalents of the compound of formula XI respectively XII and that the reaction temperature is preferably of about 0°C to 30°C.

It has now been found that the derivatives of formula I-IV (and their pharmaceutically acceptable salts if applyable) have pharmacologically and biochemically interesting properties such as Phospholipase A_2 (PLA_2) inhibition activity. The effect of the derivatives of formula I-IV of this invention on PLA_2 can be proved in vitro by taking bovine pancreatic PLA_2, 1-stearoyl-2-[C^{14}]-arachidonyl-1-phosphatidylcholine and $CaCl_2$ and adding a derivative of the formula I-IV resulting in inhibition of the PLA_2. When for example N-(5-chloro-1-naphthalenesulfonyl)-L-phenylalanine-1,6-diaminohexaneamide, i.e. compound 25 was added and a complete inhibition was designed 100%, the concentration which would bring about an inhibition of 50%, i.e. IC_{50} was 67μM.

The following examples illustrate the present invention in more detail, but they are given for illustrative purposes only and are not to be construed as limiting the invention.

Synthesis of the Precursors

Example 1

Equimolar amounts of O-benzyl-L-tyrosine and benzenesulfonyl chloride were mixed in 1N NaOH (200 mol %) and stirred for 2h. After 0.5h the desired compound precipitated. The solution was adjusted to pH 2 with 2N HCl and filtered. The precipitate was washed several times with H_2O, dried in vacuo over P_2O_5 and crystallized to yield the desired compound P1.

Substantially the same procedure as described above was repeated except that L-tryptophane was used in place of the L-tyrosine derivative to give P2.

The yields of the reactions and the analytical data of the two compounds are given in table 1.

Example 2

Equimolar amounts of L-phenylalanine and p-fluorobenzenesulfonyl chloride were mixed in 1N NaOH (200 mol %) and stirred at 60°C for 2h. The solution was adjusted to pH 2 with 2N HCl and extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered, evaporated and the residue crystallized to yield P3.

Substantially the same procedure as described above was repeated except that L-alanine (→P4), L-valine (→P5) and L-proline (→P6) were used in place of L-phenylalanine.

The yields of the reactions and the analytical data of the different compounds are given in table 1.

Example 3

To equimolar amounts of N-t-BOC-L-phenylalanine and 4-aminobiphenyl in DMF (ca 0.5M) 1-hydroxybenzotriazole (150 mol %) was added. The mixture was cooled to 0°C and DCC (110 mol %) was added in one portion. After stirring for 1h at 0°C and 1h at 25°C the reaction mixture was filtered and the DMF evaporated in vacuo. The residue was taken up in EtOAc (ca 0.1M) and washed subsequently with saturated $NaHCO_3$ solution, 2N citric acid and H_2O. After drying over $MgSO_4$, filtering and evaporation the residue was crystallized.
The compound obtained above was dissolved in CH_2Cl_2 (ca 0.4M) cooled with ice and the same amount of TFA added. After 1h the solvents were evaporated and the residue crystallized: P7.
Substantially the same procedure as described above was repeated except that N-t-BOC-L-valine (→P8) was used in place of the L-phenylalanine derivative. When N-CBZ-L-proline was used as starting material the deprotection was done by overnight hydrogenation with H_2, 10% Pd/C in EtOH (→P9). In case of N-t-BOC-L-alanine the free amine was obtained after evaporation of the solvents and stirring the residue with saturated $NaHCO_3$ solution (→P10).
The yields of the reactions and the analytical data of the different compounds are given in table 2.

Example 4

Basically the same procedure as in example 3 except that N-CBZ-piperazine [1] and N-BOC-6-aminohexane were used in place of 4-aminobiphenyl. In case of N-CBZ-piperazine N-t-BOC protected amino acids and in case of N-t-BOC-6-aminohexane N-CBZ protected amino acids were used.
Deprotection of the N-t-BOC group was done as described before with TFA/CH_2Cl_2 at 0°C (→P11,P12,P13,P14) and of the N-CBZ group with H_2, 10% Pd/C in EtOH (→P15,P16). The free amine was dissolved in acetone, equimolar amounts of oxalic acid in acetone added, the precipitate filtered and crystallized.
The yields of the reactions and the analytical data of the different compounds are given in table 2.

Synthesis of the Compounds

Example 5

To equimolar amounts of N-benzenesulfonyl-L-phenylalanine [2] and N-CBZ-piperazine [1] in DMF (ca 0.5M) 1-hydroxybenzotriazole (150 mol %) was added. The mixture was cooled to 0°C and DCC (110 mol %) was added in one portion. After stirring for 1h at 0°C and 1h at 25°C the reaction mixture was filtered and the DMF evaporated in vacuo. The residue was taken up in EtOAc (ca 0.1M) and washed subsequently with saturated $NaHCO_3$ solution, 2N citric acid and

H_2O. After drying over $MgSO_4$, filtering and evaporation of the solvent the residue was crystallized (P17).
The compound obtained above was dissolved in abs. EtOH (ca 0.1M), 10% Pd/C (10 weight %) added and stirred overnight in a H_2 atmosphere. The reaction mixture was filtered over celite and the pH of the solution adjusted to 2 with conc. HCl. Evaporation of the solvent yielded a white residue which was crystallized: 1.
Substantially the same procedure as described above was repeated except that N-benzenesulfonyl-L-alanine [3](→2) , N-benzenesulfonyl-L-valine [4](→P18 →3) and N-benzenesulfonyl-L-proline [5](→P19 →4) were used in place of N-benzenesulfonyl-L-phenylalanine.
The yields of the reactions and the analytical data of the different compounds are given in table 3 (intermediates) and table 4 and 8 (compounds).

Example 6

Basically the same procedure as in example 5 except that N-t-BOC-6-aminohexane (→P20 →5) or N-CBZ-aminopropane [6](→P21 →6) were used in place of N-CBZ-piperazine. Deprotection of the N-t-BOC group was done with TFA/CH_2Cl_2 at 0°C and of the N-CBZ group with H_2, 10% Pd/C in EtOH as described before.
The yields of the reactions and the analytical data of the two compounds are given in table 3 (intermediates) and table 4 and 9 (compounds).

Example 7

To equimolar amounts of N-benzenesulfonyl-L-phenylalanine [2] and 4-aminobiphenyl in DMF (ca 0.5M) 1-hydroxybenzotriazole (150 mol %) was added. The mixture was cooled to 0°C and DCC (110 mol %) was added in one portion. After stirring for 1h at 0°C and 1h at 25°C the reaction mixture was filtered and the DMF evaporated in vacuo. The residue was taken up in EtOAc (ca 0.1M) and washed subsequently with saturated $NaHCO_3$ solution, 2N citric acid and H_2O. After drying over $MgSO_4$, filtering and evaporation of the solvent the residue was crystallized: 7.
Substantially the same procedure as described above was repeated except that N-benzenesulfonyl-L-alanine [3](→8), N-benzenesulfonyl-L-valine [4](→9), N-benzenesulfonyl-L-proline [5](→10) and N-benzenesulfonyl-L-tryptophane P2 (→11) were used in place of N-benzenesulfonyl-L-phenylalanine.
The yields of the reactions and the analytical data of the different compounds are given in table 4,10,11 and 12.

Example 8

Basically the same procedure as in example 7 except that O-benzyl-N-benzenesulfonyl-L-tyrosine P1 was used in place of N-benzenesulfonyl-L-phenylalanine (→P22).
The compound obtained above was dissolved in p-dioxane/H_2O/HOAc 15:1:1 (ca 10mM), 10% Pd/C (10 weight %) added and the mixture stirred overnight in a H_2 atmosphere. The reaction mixture was filtered over celite and the solvents evaporated in vacuo. The residue was crystallized: 12.
The yields of the reactions and the analytical data of the two compounds are given in table 3 (intermediate) and table 4 and 10 (compound).

Example 9

To equimolar amounts of N-p-fluorobenzenesulfonyl-L-phenylalanine P3 and N-CBZ-piperazine in DMF (ca 0.5M) 1-hydroxybenzotriazole (150 mol %) was added. The mixture was cooled to 0°C and DCC (110 mol %) was added in one portion. After stirring for 1h at 0°C and 1h at 25°C the reaction mixture was filtered and the DMF evaporated in vacuo. The residue was taken up in EtOAc (0.1M) and washed subsequently with saturated $NaHCO_3$ solution, 2N citric acid and H_2O. After drying over $MgSO_4$, filtering and evaporation of the solvent the residue was crystallized: P23.
The compound obtained above was dissolved in abs. EtOH (ca 0.1M) 10% Pd/C (10 weight %) added and the mixture stirred overnight in a H_2 atmosphere. The reaction mixture was filtered over celite and the pH of the solution adjusted to 2 with conc. HCl. Evaporation of the solvent yielded a white residue which was crystallized: 13.
Substantially the same procedure as described above was repeated except that N-p-fluorobenzenesulfonyl-L-alanine P4 (→P24 →14), N-p-fluorobenzenesulfonyl-L-valine P5 (→P25 →15) and N-p-fluorobenzenesulfonyl-L-proline P6 (→P26 →16) were used in place of P3.
The yields of the reactions and the analytical data of the different compounds are given in table 3 (intermediates) and 5 and 13 (compounds).

Example 10

To equimolar amounts of N-p-fluorobenzenesulfonyl-L-phenylalanine P3 and 4-aminobiphenyl in DMF (ca 0.5M) 1-hydroxybenzotriazole (150 mol %) was added. The mixture was cooled to 0°C and DCC (110 mol %) was added in one portion. After stirring for 1h at 0°C and 1h at 25°C the reaction mixture was filtered and the DMF evaporated in vacuo. The residue was taken up in EtOAc (ca 0.1M) and washed subsequently with saturated $NaHCO_3$ solution, 2N citric acid and H_2O. After drying over $MgSO_4$, filtering and evaporation of the solvent the residue was crystallized: 17.

Substantially the same procedure as described above was repeated except that N-p-fluorobenzenesulfonyl-L-alanine P4 (→18), N-p-fluorobenzenesulfonyl L-valine P5 (→19) and N-p-fluorobenzenesulfonyl L-proline P6 (→20) were used in place of P3.
The yields of the reactions and the analytical data of the different compounds are given in table 5 and 14.

Example 11

To a concentrated solution of the amine P11 in p-dioxane and 1N NaOH (200 mol %) an equimolar amount of 5-chloro-1-naphthalenesulfonyl chloride [7,8] was added and the suspension stirred for 3h. Acidification with conc. HCl to pH 2, extraction with CH_2Cl_2 (3x), washing of the organic phase once with brine, drying over $MgSO_4$, filtering and evaporation of the solvents in vacuo yielded a residue which was purified by flash chromatography on silica gel (solvent system hexane/EtOAc 1:1).
The compound obtained above was dissolved in abs. EtOH (ca 50mM) 10% Pd/C (10 weight %) added and the mixture stirred for 3 days in a H_2 atmosphere. The reaction mixture was filtered over celite, the solvent evaporated in vacuo, the residue purified by flash chromatography on silica gel (solvent system CH_2Cl_2/MeOH 5:1) and crystallized: 21.
Substantially the same procedure as described above was repeated except that the amine P12 (→22)[2], P13 (→23)[3] or P14 (→24)[4] were used in place of the amine P11.
The yields of the reactions and the analytical data of the different compounds are given in table 6 and 15.

Example 12

To a concentrated solution of the amine P15 in p-dioxane and 1N NaOH (200 mol %) an equimolar amount of 5-chloro-1-naphthalenesulfonyl chloride was added and the suspension stirred for 3h. H_2O was added and the mixture extracted thrice with CH_2Cl_2. The organic phase was washed once with H_2O, dried over $MgSO_4$, filtered and the solvents evaporated in vacuo. Flash chromatography on silica gel (solvent system hexane/EtOAc 1:2) yielded the pure intermediate which was dissolved in CH_2Cl_2 (ca 50mM) and the same volume of TFA added. After 1h the solvents were evaporated in vacuo, the residue dissolved in a small volume of H_2O and the pH of the solution adjusted to 8 with solid $NaHCO_3$. Extraction with four portions of CH_2Cl_2/MeOH 3:1, washing of the organic phase with H_2O, drying over $MgSO_4$, filtering and evaporation of the solvents in vacuo yielded a compound which was purified by flash chromatography on silica gel (solvent system CH_2Cl_2/MeOH/conc.NH_3 20:2:1) and crystallized as HCl-salt 25.
The yield of the reaction and the analytical data of the compound are given in table 6 and 16.

[2] Solvent system for the intermediate: hexane/EtOAc 1:1; no chromatography was necessary for 22.
[3] Solvent system for the intermediate: hexane/EtOAc 1:2; solvent system for 23: CH_2Cl_2/MeOH 10:3.
[4] Solvent system for the intermediate hexane/EtOAc 1:2; no chromatography was necessary for 24

Example 13

To a concentrated solution of the amine **P7** in THF and 1N NaOH (200 mol %) an equimolar amount of 5-chloro-1-naphthalenesulfonyl chloride was added and the suspension stirred for 3h. H_2O was added and the mixture extracted thrice with CH_2Cl_2. The organic phase was washed once with H_2O, dried over $MgSO_4$, filtered and the solvents evaporated in vacuo. Flash chromatography on silica gel (solvent system hexane/EtOAc 4:1) and crystallization yielded the pure compound 26.
Substantially the same procedure as described above was repeated except that the amine **P10** (→27)[5] was used in place of the amine **P7**.
The yields of the reactions and the analytical data of the two compounds are given in table 6 and 17.

Example 14

To a concentrated solution of the amine **P8** in p-dioxane was added 1N NaOH (200 mol %). The precipitate partly dissolved after addition of a concentrated solution of an equimolar amount of 5-chloro-1-naphthalenesulfonyl chloride in THF. After 15min. the desired compound precipitated. After 2h H_2O was added and the suspension filtered, the solid dried and crystallized twice to obtain the pure compound 28.
Substantially the same procedure as described above was repeated except that the amine **P9** (→29) was used in place of the amine **P8**.
The yields of the reactions and the analytical data of the two compounds are given in table 6 and 17.

Example 15

To a concentrated solution of 4-aminobiphenyl in p-dioxane was added 1N NaOH (200 mol %) and an equimolar amount of 5-chloro-1-naphthalenesulfonyl chloride. After stirring for 2h the solvents were evaporated in vacuo. The residue was purified by flash chromatography on silica gel (solvent system hexane/EtOAc 2:1) and crystallized to yield 30.
The yield of the reaction and the analytical data of the compound are given in table 6 and 17.

Example 16

To an ice cooled suspension of 5-isoquinolinesulfonyl chloride hydrochloride [9] in CH_2Cl_2 was added NEt_3 (220 mol %). To the yellow solution the amine **P11** (90 mol %) in CH_2Cl_2 was added dropwise. After 10min. the cooling was removed and the stirring continued for 2h. The pH of the solution was adjusted to 7-8 with a saturated $NaHCO_3$ solution. The phases were separated and the organic phase washed once with H_2O, dried over $MgSO_4$, filtered and the solvent evaporated in

[5] Solvent system for 27: hexane/EtOAc 2:1.

vacuo. Flash chromatography on silica gel (solvent system CH_2Cl_2/MeOH 100:3) yielded a white foam.

A solution of the compound obtained above in 25% HBr/HOAc (8ml/mmol) was stirred under ice cooling for 5h. After addition of Et_2O (ca 40ml/mmol) the precipitate was filtered and dissolved in a few ml of H_2O. The solution was slightly basified with 1N NaOH and extracted with CH_2Cl_2/MeOH 3:1 (4x). The organic phase was washed once with H_2O, dried over $MgSO_4$, filtered and the solvents evaporated in vacuo. Flash chromatography on silica gel (solvent system CH_2Cl_2/MeOH/conc. NH_3 20:4:1) yielded a foam which was dissolved in EtOH and treated with conc. HCl to give the salt 31.

Substantially the same procedure as described above was repeated except that the amine P12 (→32)[6,7] P13 (→33) and P14 (→34)[8,9] were used in place of the amine P11.

The yields of the reactions and the analytical data of the different compounds are given in table 7 and 18.

Example 17

To an ice cooled suspension of 5-isoquinolinesulfonyl chloride hydrochloride in CH_2Cl_2 was added NEt_3 (220 mol %). To the yellow solution the amine P15 (90 mol %) in CH_2Cl_2 was added dropwise. After 10min. the cooling was removed and stirring continued for 2h. A saturated $NaHCO_3$ solution was added to adjust the pH to 7-8. The phases were separated and the organic phase washed once with H_2O, dried over $MgSO_4$, filtered and the solvent evaporated in vacuo. The residue was purified by flash chromatography on silica gel (solvent system CH_2Cl_2/MeOH 100:4).

To the compound obtained above, dissolved in CH_2Cl_2 (ca 50mM), the same volume of TFA was added. After 1h the solvents were evaporated in vacuo, the residue dissolved in a very small volume of H_2O and the pH of the solution adjusted to 8 with solid $NaHCO_3$. The H_2O phase was extracted with CH_2Cl_2/MeOH 3:1 (4x). The organic phase was dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by flash chromatography on silica gel (solvent system CH_2Cl_2/MeOH/conc. NH_3 20:4:1) and crystallized as HCl-salt 35.

The yield of the reaction and the analytical data of the compound are given in table 7 and 16.

Example 18

To an ice cooled suspension of 5-isoquinolinesulfonyl chloride hydrochloride in CH_2Cl_2 was added NEt_3 (220 mol %). To the yellow solution the amine P7 (90 mol %) was added dropwise. After 10min. the cooling was removed and stirring continued for 2h. The pH of the solution was adjusted

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6 Solvent system for the intermediate: CH_2Cl_2/MeOH 100:4.

7 32 in EtOH was treated with conc. HCl. The precipitate was filtered and thoroughly washed with EtOH. The salt could not be crystallized.

8 Solvent system for the intermediate: CH_2Cl_2/MeOH 100:5.

9 34 was not purified by flash chromatography but directly crystallized as HCl-salt.

to 7-8 with a saturated $NaHCO_3$ solution. The phases were separated and the organic phase washed once with H_2O, dried over $MgSO_4$, filtered and the solvent evaporated in vacuo. Flash chromatography on silica gel (solvent system CH_2Cl_2/MeOH 100:3) yielded a white solid which was crystallized to give 36.
Substantially the same procedure as described above was repeated except that the amine P8 (→37), P9 (→38)[10], P10 (→39)[11] and (+)-P9 (→40) were used in place of the amine P7.
The yields of the reactions and the analytical data of the different compounds are given in table 7 and 19.

Example 19

Substantially the same procedure as described in example 18 was used except that 4-aminobiphenyl (→41)[12] and 4-aminobenzol (→42) were used in place of the amine P7.
The yields of the reaction and the analytical data of the two compounds are given in table 7 and 19.

Enzyme Assay

Phospholipase A_2 (PLA_2) activity was measured using bovine pancreatic PLA_2 as the enzyme and a sonicated dispersion of 1-stearoyl-2-[C^{14}]-arachidonyl-phosphatidylcholine (56mCi/mmol) as the substrate in the following manner [11,12]: 60ng bovine pancreatic PLA_2 was mixed and incubated with buffer and inhibitors (100mM Tris, pH 8; 100mM $CaCl_2$; 20mM EDTA, pH 8) at 37°C for 10min. to allow interaction between the enzyme and the drugs. The substrate (38nCi) in buffer and 0.3% cholate was added to initiate the reaction which continued for 20min. at 37°C. The total reaction volume was 0.1ml. The reaction was stopped by adding 0.1ml of an ice cold EtOH/HOAc 98:2 mixture. Released arachidonic acid was separated from the unreacted substrate via thin layer chromatography on silica gel (solvent system $CHCl_3$/MeOH/H_2O 14:6:1). The radioactivity of the two spots was quantified using a bioscanner.
Inhibitors were dissolved in buffer[13] and tested in duplicate within each experiment, and each inhibitor was tested in at least two experiments. When necessary, inhibitors were dissolved in DMSO[14]. The % inhibition at a given concentration was combined for several experiments and the IC_{50} determined from a semilog plot of % inhibition vs concentration. Under the condition described the rate of hydrolysis was 20-25% of the substrate being hydrolyzed in absence of inhibitors. The results are listed in table 20.

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[10] Solvent system for 38 and 40: CH_2Cl_2/MeOH 100:2.
[11] Solvent system for 39: CH_2Cl_2/MeOH 100:5.
[12] Solvent system for 41 and 42: CH_2Cl_2/MeOH 100:2.
[13] 0.01ml inhibitor solution were used in these experiments.
[14] 0.005ml inhibitor solution were used in these experiments (= 5 vol %).

Literature

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[12] W.C.Ripka et al. J.Cell.Biochem. 40,279 (1989)

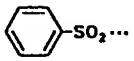
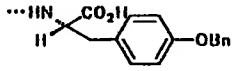
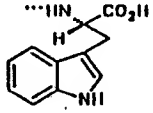
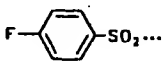
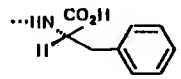
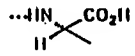
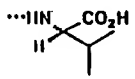
Table 1		mp, [°C] (cryst. from)	$[\alpha]_D^{20}$, [°]	yield [%]	analysis	MS, m/e [%]	ID
		150-151 (EtOH)	+0.27 (c=1.11,acetone)	63.5	$C_{22}H_{21}NO_5S$ * 0.5 H_2O * 0.5 EtOH (C,H,N)	411 (49)	P1
		153-154 (EtOH)	+36.5 (c=1.07,DMSO)	50.1	$C_{17}H_{16}N_2O_4S$	344 (27)	P2
		118-119 (Et_2O,pet.ether)	+5.8 (c=1.18,EtOH)	57.8	$C_{15}H_{14}FNO_4S$ (C,H,N)	323 (0.1)	P3
		109-110 (Et_2O,pet.ether)	-3.9 (c=1.42,EtOH)	58.9	$C_9H_{10}FNO_4S$ (C,H,N)	247 (0.1)	P4
		126-127 (Et_2O,pet.ether)	+23.1 (c=1.43,EtOH)	64.5	$C_{11}H_{14}FNO_4S$ (C,H,N)	275 (1)	P5
		116-117 (Et_2O,pet.ether)	-81.9 (c=1.5,EtOH)	77.3	$C_{11}H_{12}FNO_4S$ (C,H,N)	273 (0.1)	P6

Table 2

	R	mp. [°C] (cryst. from)	$[\alpha]_D^{20}$, [°]	yield [%]	analysis	MS, m/e [%]	ID
	BOC	186-187 (acetone)	-6.9 (c=0.62,$CHCl_3$)	66.4	$C_{24}H_{28}N_2O_3$ (C,H,N)	416 (24)	
	H	213-214 (acetone,Et_2O, pet.ether)	+15.1 (c=0.69,acetone)	72.5	$C_{21}H_{20}N_2O$ *CF_3COOH (C,H,N)	316 (9)	P7
	BOC	180-182 (EtOAc,hexane)	-33.3 (c=0.91,$CHCl_3$)	58.3	$C_{22}H_{28}N_2O_3$ (C,H,N)	368 (0.2)	
	H	190-191 (EtOH,pet.ether)	-71.4 (c=0.57,acetone)	67.5	$C_{17}H_{20}N_2O$ *CF_3COOH (C,H,N)	268 (10)	P8
	H	156-157 (EtOH)	-54.0 (c=0.79,$CHCl_3$)	54.7	$C_{17}H_{18}N_2O$ (C,H,N)	266 (42)	P9
	BOC	159-160 (EtOAc)	-63.1 (c=1.1,$CHCl_3$)	69.6	$C_{20}H_{24}N_2O_3$ (C,H,N)	340 (0.2)	
	H	217-218 (MeOH)	+7.5 (c=0.27,DMSO)	100	$C_{15}H_{16}N_2O$ *$(COOH)_2$ *0.25 MeOH (C,H,N)	240 (13)	P10

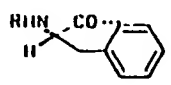
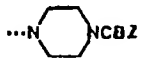
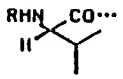
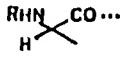
Table 2 cont.		R	mp, [°C] (cryst. from)	$[\alpha]_D^{20}$, [°]	yield [%]	analysis	MS, m/e [%]	ID
		H	181-183 (EtOH)	+26.9 (c=0.525,DMSO)	58.1	$C_{21}H_{25}N_3O_3$ * 0.75 $(COOH)_2$ (C,H,N)	367 (0.1)	P11
		BOC	104-105 (acetone,pet.ether)	+27.1 (c=0.95,$CHCl_3$)	65.1	$C_{22}H_{33}N_3O_5$ (C,H,N)	419 (0.1)	
		H	153-154 (acetone)	+17.3 (c=1.04,H_2O)	78.2	$C_{17}H_{25}N_3O_3$ * 0.5 $(COOH)_2$		P12
		BOC	109-110 (acetone,pet.ether)	-9.7 (c=0.65,$CHCl_3$)	84.6	$C_{22}H_{31}N_3O_5$ (C,H,N)	417 (0.3)	
		H	141-142 (EtOH)	-21.6 (c=0.58,acetone)	81.3	$C_{17}H_{23}N_3O_3$ * $(COOH)_2$ (C,H,N)		P13
		H	193-194 (MeOH)	+4.9 (c=0.88,DMSO)	79.7	$C_{15}H_{21}N_3O_3$ * $(COOH)_2$ (C,H,N)		P14

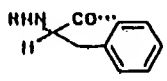
Table 2 cont.		R	mp, [°C] (cryst. from)	$[\alpha]_D^{20}$, [°]	yield [%]	analysis	MS, m/e [%]	ID
	···HN(CH$_2$)$_6$NHBOC	CBZ	126-127 (acetone)	+4.5 (c=1.15,CHCl$_3$)	57.4	$C_{28}H_{39}N_3O_5$ (C,H,N)	497 (0.1)	
		II	142-143 (EtOH)	+31.9 (c=0.74,MeOH)	100	$C_{20}H_{33}N_3O_3$ * $(COOH)_2$ * 0.3 H_2O (C,H,N)		P15
		CBZ	95-96 (acetone)	-56.9 (c=1.2,CHCl$_3$)	67.7	$C_{24}H_{37}N_3O_5$ (C,H,N)	447 (0.2)	
		II	163-164 (EtOH)	-25.1 (c=0.71,DMSO)	85.0	$C_{16}H_{31}N_3O_3$ * $(COOH)_2$ (C,H,N)		P16

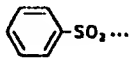
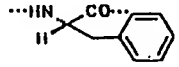
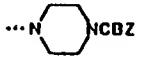
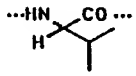
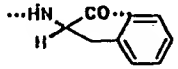
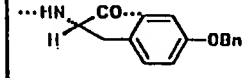
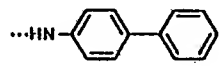
Table 3			mp, [°C] (cryst. from)	$[\alpha]_D^{20}$, [°]	yield [%]	analysis	MS, m/e [%]	ID
			116-117 (EtOH,pet.ether)	+81.2 (c=1.08,$CHCl_3$)	82.0	$C_{27}H_{29}N_3O_5S$ (C,H,N)	507 (1)	P17
			119-120 (EtOH)	+77.6 (c=1.0,$CHCl_3$)	81.0	$C_{21}H_{29}N_3O_5S$ (C,H,N)	459 (1)	P18
			158-160 (EtOH)	-29.0 (c=1.0,$CHCl_3$)	44.0	$C_{21}H_{27}N_3O_5S$ (C,H,N)	457 (1)	P19
		···HN(CH₂)₆NHBOC	154-155 (acetone)	+18.0 (c=0.56,DMSO)	81.5	$C_{26}H_{37}N_3O_5S$	503 (6)	P20
		···HN(CH₂)₃NHCBZ	135-136 (acetone,pet.ether)	-24.7 (c=0.785,$CHCl_3$)	59.0	$C_{26}H_{29}N_3O_5S$ (C,H,N)	495 (0.1)	P21
			211-212 (acetone)	+81.9 (c=0.81,DMSO)	59.9	$C_{34}H_{30}N_2O_4S$ (C,H,N)	562 (12)	P22

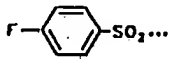
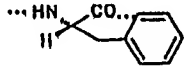
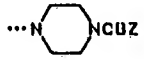
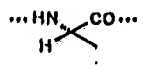
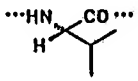
Table 3 cont.			mp, [°C] (cryst. from)	$[\alpha]_D^{20}$, [°]	yield [%]	analysis	MS, m/e [%]	ID
			104-105 (EtOH,pet.ether)	+73.0 (c=1.22,$CHCl_3$)	86.1	$C_{27}H_{28}FN_3O_5S$ (C,H,N)	525 (0.3)	P23
			97-98 (EtOH,pet.ether)	+36.8 (c=0.86,$CHCl_3$)	79.7	$C_{21}H_{24}FN_3O_5S$ * 0.5 C_6H_{14} (C,H,N)	449 (4)	P24
			156-157 (EtOH)	-12.0 (c=1.4,$CHCl_3$)	66.5	$C_{23}H_{26}FN_3O_5S$ (C,H,N)	475 (0.1)	P25
			102-103 (t-amylalcohol)	+63.7 (c=0.56,DMSO)	71.0	$C_{23}H_{28}FN_3O_5S$ * 0.25 t-amylalcohol (C,H,N)	477 (28)	P26

Table 4

ID	MS, m/e [%]	analysis	yield [%]	$[\alpha]_D^{20}$, [°]	mp. [°C] (cryst. from)			
1		$C_{19}H_{21}N_3O_3S * HCl$ (C,H,N)	81.5	+63.3 (c=2.095,H_2O)	231-233 (MeOH,Et_2O)			
2		$C_{13}H_{19}N_3O_3S * HCl * 0.25\ H_2O$ (C,H,N)	80.1	-4.7 (c=0.725,H_2O)	203-204 (EtOH,Et_2O)			
3		$C_{15}H_{21}N_3O_3S * HCl$ (C,H,N)	58.1	+34.3 (c=1.515,H_2O)	248-250 (EtOH,Et_2O)			
4		$C_{15}H_{21}N_3O_3S * HCl$ (C,H,N)	78.8	-135.6 (c=1.72,H_2O)	282-284 dec (EtOH)			
5		$C_{21}H_{29}N_3O_3S * HCl$ (C,H,N)	81.0	+0.1 (c=0.955,H_2O)	123-124 (MeOH,Et_2O)			
6		$C_{18}H_{23}N_3O_3S * HCl$ (C,H,N)	81.0	-42.6 (c=0.655,EtOH)	150-152; sinters at ca 80° (amorphous)			

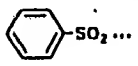
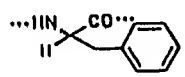
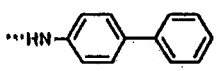
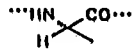
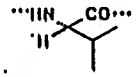
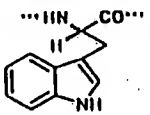
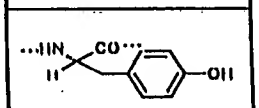
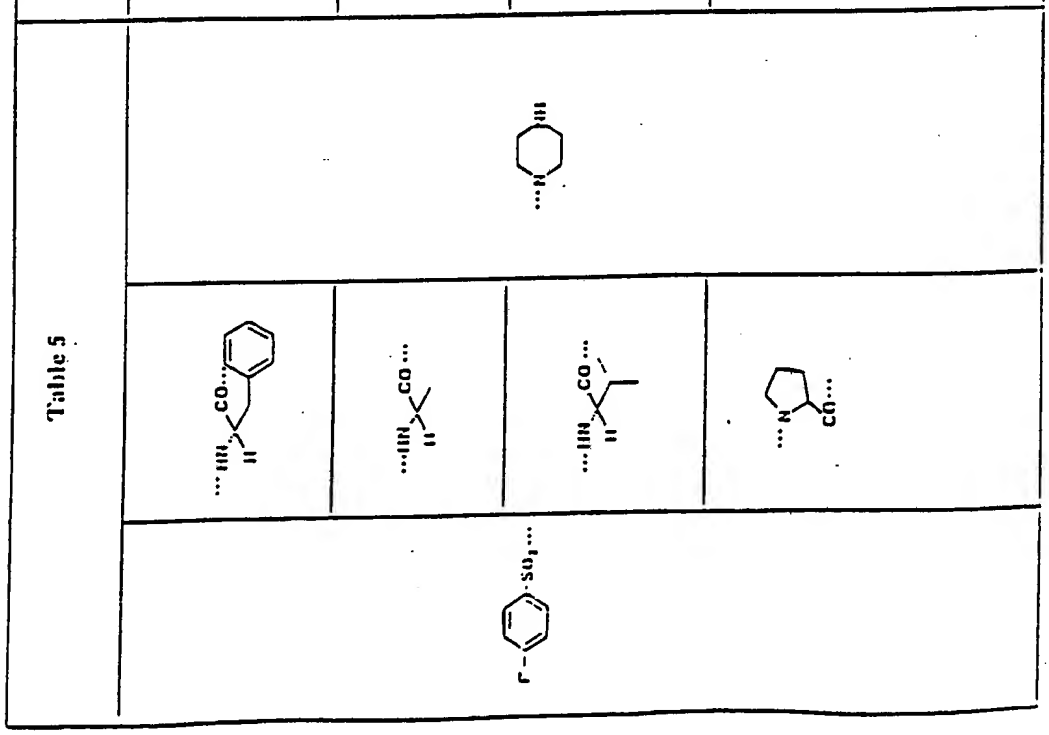
Table 4 cont.			mp, [°C] (cryst. from)	$[\alpha]_D^{20}$, [°]	yield [%]	analysis	MS, m/e [%]	ID
			200-202 (EtOH)	+15.4 (c=0.62,acetone)	72.4	$C_{27}H_{24}N_2O_3S$ (C,H,N)	456 (39)	7
			178-180 (EtOH)	-75.6 (c=0.6,acetone)	55.5	$C_{21}H_{20}N_2O_3S$ (C,H,N)	380 (29)	8
			226-227 (EtOH)	-12.7 (c=0.94,acetone)	54.4	$C_{23}H_{24}N_2O_3S$ (C,H,N)	408 (28)	9
			212-214 (EtOH)	-224.0 (c=0.26,acetone)	62.9	$C_{23}H_{22}N_2O_3S$ (C,H,N)	406 (14)	10
			219-221 (EtOH)	+73.4 (c=0.56,DMSO)	51.1	$C_{29}H_{25}N_3O_3S$ (C,H,N)	495 (74)	11
			222-223 (EtOH)	+92.3 (c=1.23,DMSO)	65.1	$C_{27}H_{24}N_2O_4S$ * 0.25 EtOH (C,H,N)	472 (53)	12

Table 5



ID	MS, m/e [%]	analysis	yield [%]	$[\alpha]_D^{20}$, [°]	mp. [°C] (cryst. from)
13		$C_{19}H_{22}FN_3O_3S * HCl$ (C,H,N)	51.0	+44.0 (c=1.65,H_2O)	227-229 (MeOH,Et_2O)
14		$C_{13}H_{18}FN_3O_3S * HCl$ (C,H,N)	51.0	-15.8 (c=1.16,H_2O)	218-219 (EtOH,Et_2O)
15		$C_{15}H_{22}FN_3O_3S * HCl$ * 0.5 MeOH (C,H,N)	60.4	+19.5 (c=1.24,H_2O)	194-195 (MeOH,Et_2O)
16		$C_{15}H_{20}FN_3O_3S * HCl$ (C,H,N)	87.6	-127.6 (c=1.36,H_2O)	278-280 (EtOH)

Table 5 cont.

									ID
			179-180 (EtOH)	+27.0 (c=1.42,acetone)	68.4	$C_{27}H_{23}FN_2O_3S$ (C,H,N)	474 (67)	17
			220-222 (EtOH)	-63.7 (c=0.765,acetone)	67.6	$C_{21}H_{19}FN_2O_3S$ (C,H,N)	398 (14)	18
			243-244 (EtOH)	-1.9 (c=1.035,acetone)	51.5	$C_{23}H_{23}FN_2O_3S$ (C,H,N)	426 (41)	19
			219-220 (EtOH)	-182.7 (c=1.55,acetone)	52.1	$C_{23}H_{21}FN_2O_3S$ (C,H,N)	424 (22)	20

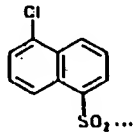
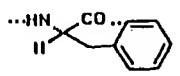
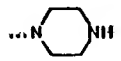
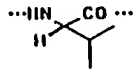
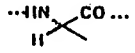
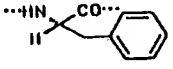
Table 6			mp, [°C] (cryst. from)	$[\alpha]_D^{20}$, [°]	yield [%]	analysis	MS, m/e [%]	ID
			229-230 dec (t-amylalcohol)	-84.1 (c=0.31,H_2O)	25.8	$C_{23}H_{24}ClN_3O_3S$ * HCl * 0.5 t-amylalcohol (C,H,N)		21
			164-166 (EtOH,Et_2O)	+76.3 (c=0.46,H_2O)	13.1	$C_{19}H_{24}ClN_3O_3S$ * 0.5 EtOH * 0.5 H_2O (C,H,N)		22
			235-239 (EtOH,Et_2O)	-48.4 (c=0.75,H_2O)	21.1	$C_{19}H_{22}ClN_3O_3S$ * HCl *0.25 Et_2O (C,H,N)		23
			285-287 (H_2O,acetone)	-67.2 (c=1.07,DMSO)	17.4	$C_{17}H_{20}ClN_3O_3S$ * 0.25 acetone * 0.25 H_2O (C,H,N)		24
			228-230 dec (t-amylalcohol, Et_2O)	-29.0 (c=0.21,H_2O)	9.2	$C_{25}H_{30}ClN_3O_3S$ * HCl * 0.5 t-amylalcohol (C,H,N)		25

Table 6 cont.

			190-192 (EtOAc)	+44.5 (c=0.89,DMSO)	51.0	$C_{31}H_{25}ClN_2O_3S$ (C,H,N)	540 (65)	26
			186-187 (EtOAc)	-9.7 (c=0.775,acetone)	43.4	$C_{25}H_{21}ClN_2O_3S$ (C,H,N)	464 (40)	27
			218-219 (acetone,hexane)	+47.9 (c=0.94,acetone)	64.5	$C_{27}H_{25}ClN_2O_3S$ (C,H,N)	492 (28)	28
			180-181 (EtOH)	-104.0 (c=0.64,acetone)	54.4	$C_{27}H_{23}ClN_2O_3S$ (C,H,N)	490 (14)	29
			192-193 (EtOH)	—	77.3	$C_{22}H_{16}ClNO_2S$ (C,H,N)	393 (40)	30
			135-136 (EtOH) LiI [10]: 138 (EtOH,H_2O)	—	77.6	$C_{16}H_{12}ClNO_2S$ (C,H,N)	317 (56)	43 LiI[10]

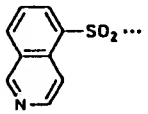
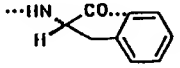
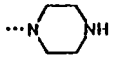
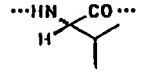
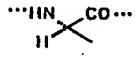
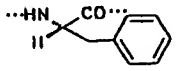
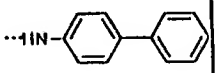
Table 7			mp, [°C] (cryst. from)	$[\alpha]_D^{20}$, [°]	yield [%]	analysis	MS, m/e [%]	ID
			238-240 dec (EtOH, t-amyl-alcohol)	-58.2 (c=0.3,H_2O)	21.4	$C_{22}H_{24}N_4O_3S$ * 2HCl *H_2O (C,H,N)		31
			267-269 dec (amorphous)	+66.4 (c=0.42,DMSO)	13.4	$C_{18}H_{24}N_4O_3S$ * 2HCl * 0.5 EtOH * H_2O (C,H,N)		32
			235-237 dec (EtOH,Et_2O, t-amylalcohol)	-21.3 (c=0.23,H_2O)	16.9	$C_{18}H_{22}N_4O_3S$ * 2HCl		33
			240-242 dec (MeOH,Et_2O)	+36.4 (c=1,43,H_2O)	11.9	$C_{16}H_{20}N_4O_3S$ * 2HCl * 0.5 MeOH * H_2O (C,H,N)		34
		···HN(CH$_2$)$_6$NH$_2$	253-255 dec (t-amylalcohol)	-112.7 (c=0.73,H_2O)	33.5	$C_{24}H_{30}N_4O_3S$ * 2HCl * 0.25 t-amylalcohol (C,H,N)		35
			115-116 (acetone)	+21.8 (c=1.13,acetone)	24.1	$C_{30}H_{25}N_3O_3S$ * acetone (C,H,N)	507 (21)	36

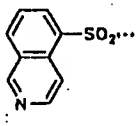
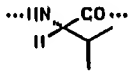
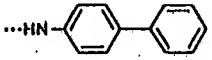
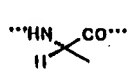
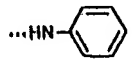
Table 7 cont.			mp, [°C] (cryst. from)	$[\alpha]_D^{20}$, [°]	yield [%]	analysis	MS, m/e [%]	ID
			224-225 (acetone,pet.ether)	+95.4 (c=0.87,acetone)	25.7	$C_{26}H_{25}N_3O_3S$ (C,H,N)	459 (37)	37
			170-172 (EtOH)	-113.5 (c=0.965,acetone)	59.4	$C_{26}H_{23}N_3O_3S$ (C,H,N)	457 (35)	38
			185-186 (acetone,pet.ether)	+22.8 (c=0.63,acetone)	38.4	$C_{24}H_{21}N_3O_3S$ (C,H,N)	431 (35)	39
			178-179 (EtOH)	+113.2 (c=1.095,acetone)	58.8	$C_{26}H_{23}N_3O_3S$ (C,H,N)	457 (32)	40
			174-175 (acetone,pentane)	—	32.8	$C_{21}H_{16}N_2O_2S$ (C,H,N)	360 (53)	41
			154-155 dec (acetone,Et_2O)	—	32.1	$C_{15}H_{12}N_2O_2S$ (C,H,N)	284 (49)	42

Table 8: ^{1}H-NMR (300 MHz, D_2O)

ID	H-C(2) H-C(6)	H-C(3) H-C(5)	H-C(4)	H-C(1')	H-C(2')	H-C(3')	H-C(5') H-C(6') H-C(7')	H_3C-C(1')	H_3C-C(2')	H-C(4')/ H-C(8')	H-C(1'') H-C(2'') H-C(3'') H-C(4'')
1	7.82 m	7.62 m	7.73 m	4.52 dxd (9.84,6.10)	3.06,2.91 2dxd (12.97,6.06) (12.96,9.88)		7.36 m			7.20 m	1.73 (1) 2.67 (1) 2.85 (1) 2.93-3.01 (2) 3.24 (1) 3.35 (1) 3.68 (1) all m
2	7.88 m	7.67 m	7.76 m	4.43 q (6.96)				1.28 d (6.96)			3.01 (1) 3.16 (1) 3.23 (1) 3.31 (1) 3.56 (2) 3.80 (2) all m
3	7.87 br d	7.66 m	7.76 br t	4.05 d (6.78)	1.93 "sextet"				0.89,0.93 2d (6.72,6.76)		2.89 (1) 3.01 (1) 3.14-3.27 (2) 3.43-3.60 (2) 3.68 (1) 3.80 (1) all m
4	7.90 m	7.69 m	7.79 m	4.69 m	1.71 (1) 1.90 (2) 2.15 (1) m					3.30-3.42 (5) 3.55 (1) 3.81 (1) 3.89-4.07 (3) all m	

Table 9; ^{1}H-NMR (300 MHz, D_2O)

ID	H-C(2) H-C(6)	H-C(3) H-C(5)	H-C(4)	H-C(1')	H-C(4')/ H-C(8')	H-C(5') H-C(6') H-C(7')	H-C(2')	H-C(1'') H-C(2'') H-C(3'') H-C(4'') H-C(5'') H-C(6'')
5	7.72 2br d	7.54 br t	7.67 br t	3.94 t (7.75)	7.11 m	7.26 m	1.05 (2) 1.18-1.28 (4) 1.60 (2) 2.74 (1) 2.84-2.99 (5) all m	
6	7.72 2br d	7.55 br t	7.68 br t	3.95 t (7.83)	7.11 m	7.27 m	2.92 (2) d (7.98)	1.60 br q (2) 2.60 (2) 2.91 (1) 3.02 (1) m

Table 10: ^{1}H-NMR (300 MHz, acetone-d_6 (7) or DMSO-d_6 (12))

ID	H-C(3) H-C(5)	H-C(4)	H-C(2'') H-C(6'')	H-C(10'')	H-C(9'') H-C(11'')	H-C(3'') H-C(5'')	H-C(2) H-C(6)	H-C(8'') H-C(12'')
7	7.48-7.58 (5) m			7.33 br t	7.44 (4) m		7.77 br d	7.63 br d
12	7.35-7.53 (8) m					7.61 d (8.55)	7.68 (4) m	

ID	H-C(1')	H-C(2')	H-C(4')/ H-C(8')	H-C(5') H-C(6') H-C(7')	$NHSO_2$-	NHCO..
7	4.29 br t	2.94,3.12 2dxd (13.70,7.85) (13.70,6.58)	7.20 (5) m		6.97 br s	9.29 s
12	4.07 m	2.71,2.90 2dxd (13.55,8.63) (13.61,6.14)	7.02 br d	6.66 (2) d (8.29)		10.36 brs

Table 11: ^{1}H-NMR (300 MHz, acetone-d_6)

ID	H-C(2) H-C(6)	H-C(3) H-C(5)	H-C(4)	H-C(8'') H-C(12'')	H-C(3'') H-C(5'')	H-C(2'') H-C(6'')	H-C(9'') H-C(11'')	H-C(10'')	H-C(1')
8	7.93 2br d	7.53-7.65 (9) m					7.44 br t	7.33 br t	4.08 q (7.06)
9	7.88 m	7.41-7.64 (11) m						7.33 br t	3.81 m
10	7.97 2br d	7.82 2br d	7.77 m	7.70 2d	7.66 (4) m		7.46 2br t	7.34 br t	4.27 m

ID	H-C(2')	H-C(3')	H-C(4')/ H-C(8')	H-C(5') H-C(6') H-C(7')	H_3C-C(1')	H_3C-C(2')	$NHSO_{3^-}$	$NHCO_{..}$
8					1.33 d (7.06)		6.98 br s	9.31 s
9	2.08 m					0.96,0.97 2d (6.75,6.79)	6.71 d (9.08)	9.33 br s
10	1.66,1.81,1.93,2.11 (4) m		3.34,3.64 2dxdxd (9.98,7.92,6.95 (10.0,6.94,4,26					9.41 s

Table 12: ^{1}H-NMR (300 MHz, DMSO-d_6)

ID	H-C(2) H-C(6)	H-C(8") H-C(12")	H-C(3) H-C(5)	H-C(4"")	H-C(7"")	H-C(4)	H-C(9") H-C(11")	H-C(10")
11	7.68,7.72 (4) 2brd		7.49 (4) m			7.38 (4) brt		

ID	H-C(1')	H-C(2')	H-C(2"")	H-C(5"")	H-C(6"")	H-C(3") H-C(5")	H-C(2") H-C(6")	NH...
11	4.26 brt	3.12,3.29 2dxd (14.45,7.02) (14.45,6.80)	7.16 brs	6.98 dxd (7.55,7.19)	7.10 t (7.48)	7.58 (4) m		10.97 brs

Table 13: ^{1}H-NMR (300 MHz, D_2O)

ID	H-C(2) H-C(6)	H-C(3) H-C(5)	H-C(1')	H_3C-C(1')	H_3C-C(2')	H-C(3')	H-C(2')	H-C(1'') H-C(2'') H-C(3'') H-C(4'')	H-C(4')/ H-C(8')	H-C(5') H-C(6') H-C(7')
13	7.82 m	7.20 m	4.53 dxd (9.38,6.47)				1.84 (1) 2.65 (1) 2.89-3.12 (5) 3.37 (1) 3.47 br d (1) 3.78 br d (1) all m		7.33 (5) m	
14	7.92 2br d	7.38 m	4.45 q (6.95)	1.28 d (6.95)				3.12 (1) 3.22-3.37 (3) 3.63-3.68 (2) 3.80-3.90 (2) all m		
15	7.91,7.92 2br d	7.38 br t	4.07 d (6.75)		0.87,0.93 2d (6.70,6.75)		1.94 "soxtet"	3.03 (1) 3.12-3.31 (3) 3.50 (1) 3.63-3.78 (2) 3.88 (1) all m		
16	7.94 2br d	7.40 br t	4.71 m			1.73 (1) 1.92 (2) 2.19 (1) m		3.33-3.44 (5) 3.54 (1) 3.81-3.87 (1) 3.91-4.07 (3) all m		

Table 14: ^{1}H-NMR (300 MHz, acetone-d_6)

II	II-C(2) II-C(6)	II-C(3) II-C(5)	II-C(1')	II-C(2')	II-C(3')	II-C(4')/ II-C(8')	II-C(5') II-C(6') II-C(7')	H_3C-C(1')
17	7.79 2br d	7.11 m	4.26 dxd (8.45,6.25)	2.96,3.14 2dxd (13.73,8.45) (13.73,6.19)	7.19 (5) m			
18	7.97 2br d	7.30 br d	4.10 q (7.06)					1.35 d (7.06)
19	7.95,7.93 2br d (9.06) (9.04)	7.23,7.20 2br d	3.80 m	2.08 m				
20	8.05 2br d	7.81 br d	4.28 m	1.71,1.84-2.00,2.13 (4) m		3.63,3.35 2dxdxd (9.99,6.94,4.64 (9.87,7.91,6.76		

Table 14 cont.:

ID	H,C-C(2')	H-C(8'') H-C(12'')	H-C(3'') H-C(5'')	H-C(2'') H-C(6'')	H-C(9'') H-C(11'')	H-C(10'')	$NHSO_2$-	$NHCO_2$
17		7.61 br d	7.55 (4) br s		7.43 br t	7.32 br t		9.29 s
18		7.58-7.65 (6) m			7.45 br t	7.33 br t	7.06 br s	9.34 s
19	0.97 (6) d (6.84)	7.63 m	7.56 (4) m		7.45 2br t	7.33 br t	6.83 m	9.42 br s
20		7.65 (4) m		7.45 (4) m		7.34 br t		9.41 s

Table 15: ^{1}H-NMR (300 MHz, DMSO-d_6 (21), D_2O)

ID	H-C(2)	H-C(3)	H-C(7)	H-C(8)	H-C(4)	$NHSO_{2-}$	H-C(6)	H-C(1')
21	8.63 d (8.83)	8.04 dxd (9.19,7.72)	7.73,7.58 * 2dxd (8.09,7.73)	8.46,8.19 * 2d (8.09,8.46)	7.69 m		8.12,7.86 * 2d (7.36,7.35)	4.37 t (7.36)
22	8.56 d (8.46)	7.65 dxd (8.09,7.72)	7.80 br dxd (8.09,7.36)	8.25 d (7.36)	7.72 d (7.35)	7.68 br s	8.08 d (7.72)	3.91 d (7.35)
23	8.63 d (8.49)	7.65-7.80 m		8.26 m			8.09 d (8.08)	5.00 m
24	8.58 br d (8.24)	7.66 dxd (7.88,7.77)	7.72 dxd (7.50)	8.26 br d (7.45)	7.80 dxd (7.74,1.42)	8.24 s	8.09 br d (7.98)	4.37 q (6.96)

* doubling of the signals

Table 15 cont.:

ID	H-C(3')	H-C(2')	H-C(1'') H-C(2'') H-C(3'') H-C(4'')	H-C(4')/ H-C(8')	H-C(5') H-C(6') H-C(7')	H_3C-C(1')	H_3-C(2')
21		2.00 (1) 2.36 (2) 2.66-2.83 (3) 3.03 (2) 3.19-3.33 (2) all m		7.13 (2) m	7.06 m		
22		1.86 "sextet"	2.63 (1) 2.81 (1) 3.05 (3) 3.25-3.42 (2) 3.64 (1) all m				0.82,0.85 2d
23	1.85-2.05 (3) 2.27 (1) m		3.13 (1) 3.26 (3) 3.54-3.91 (6) all m				
24			2.73 (1) 2.89 (1) 3.05-3.27 (4) 3.51-3.62 (2) all m			1.21 d (6.98)	

Table 16: ^{1}H-NMR (300 MHz, D_2O)

ID	II-C(1)	II-C(2)	II-C(7)	II-C(3)	II-C(4)	II-C(6)	II-C(8)
25		8.63 d (8.38)	7.65-7.80 m		7.90 m	8.09 d (7.82)	8.25 d (7.39)
35	9.66 s		8.02 dxd (8.09,7.72)	8.52 m		8.61 2d (7.72)	

ID	II-C(1')	II-C(4') II-C(5') II-C(6') II-C(7') II-C(8')	II-C(2')	II-C(1'') II-C(6'')	II-C(2'') II-C(3'') II-C(4'') II-C(5'')	NH,
25	3.88 "t" (7.38)	6.87 (5) m	3.02-3.13 (6) m		1.45 (6) 1.77 (2) m	
35	3.88 dxd (11.40,4.41)	6.68 (5) m	2.96,2.62 2dxd (14.52,4.23) (14.13,11.21)	3.16,3.02 (4) m	1.32-1.55 (6) 1.69 (2) m	8.36 br t

Table 17: ^{1}H-NMR (300 MHz, acetone-d_6, $CDCl_3$ (43))

ID	H-C(2)	H-C(3)	H-C(4)	H-C(6)	H-C(8)	H-C(7)	H-C(1')	H-C(2')	H-C(3')	H-C(4')/ H-C(8')
26	8.67 br d (8.72)	7.62 dxd (8.69,7.52)	7.75 dxd (7.52,0.94)	8.21 dxd (7.36,1.18)	8.37 br d (8.55)	7.60 dxd (8.57,7.35)	4.24 dxd (9.02,5.73)	2.85,3.07 2dxd (13.80,9.02) (13.80,5.73)		7.01 m
27	8.84 br d (8.67)	7.70 dxd (8.64,7.57)	7.80 br d (7.51)	8.38 dxd (7.35,1.14)	8.46 br d (8.56)	7.73 dxd (8.53,7.39)	4.10 q (7.06)			
28	8.85 d (8.60)	7.68 dxd (8.44,7.54)	7.76 dxd (7.48,1.06)	8.36 2br d		7.67 dxd (8.53,7.26)	3.72 d (7.32)	2.00 m		
29	8.97 br d (8.72)	7.71 dxd (8.72,7.56)	7.82 dxd (7.50,0.96)	8.44 dxd (7.40,1.12)	8.58 br d (8.55)	7.82 dxd (8.54,7.43)	4.50 m	1.84,2.06,2.14 m		3.63 m
30	8.86 d (8.70)	7.71 dxd (8.52,7.71)	7.82 d (7.40)	8.42 br d (7.35)	8.56 d (8.57)	7.78 dxd (8.36,7.35)				
43	8.67 br d (8.82)	7.56 dxd (8.82,7.36)	7.69 dxd (7.35,1.10)	8.27 dxd (7.35,1.10)	8.54 br d (8.46)	7.57 dxd (8.45,7.35)				

Table 17 cont.:

ID	H-C(5') H-C(6') H-C(7')	H_2C-C(1')	H_2C-C(2')	H-C(3") H-C(5")	H-C(2") H-C(6")	H-C(9") H-C(11")	H-C(8") H-C(12")	H-C(10")	NHCO-	NH_2SO_2-
26	6.92 m			7.44-7.54 m			7.64 br d	7.34 br t	9.22 s	
27		1.28 d (7.06)		7.37 m	7.51 br d	7.44 br t	7.62 2d	7.33 br t	9.09 s	
28			0.84,0.92 2d (6.72)	7.24 m	7.46 m		7.61 2d	7.33 br t	9.07 br s	7.15 br s
29				7.56 m		7.45 br t	7.64 2d	7.33 br t	9.13 s	
30				7.47 br d (8.60)	7.22 br d (8.61)	7.39 br t	7.52 br d (7.27)	7.29 br t		9.61 s
43						7.04-7.14 m		6.93 m [H-C(4")]		6.93 m

Table 18: ^{1}H-NMR (300 MHz, D_2O)

ID	H-C(1)	H-C(3)	H-C-(4)	H-C(8)	H-C(6)	H-C(7)	H-C(1')
31	9.72 s	8.59 s		8.65 2br d		8.05 "t"	4.43 dxd (10.30,5.89)
32	9.85 s	9.06 d (6.99)	8.78 d (6.99)	8.77 d (7.73) 8.82 dxd (8.45,1.10)		8.16 "t" (8.09)	4.11 d (6.98)
33	9.83 s	9.10 d (6.91)	8.75 m		8.81 d (7.47)	8.16 "t" (7.94)	5.01 m
34	9.71 s	8.85 d (6.77)	8.71 d (6.77)	8.65 d (8.31)	8.69 d (7.50)	8.05 "t" (7.90)	4.51 q (7.03)

Table 18 cont.:

ID	H-C(2')	H-C(3')	H-C(5') H-C(6') H-C(7')	H-C(4')/ H-C(8')	H-C(1'') H-C(2'') H-C(3'') H-C(4'')	H_3C-C(1')	H_3C-C(2')
31	2.74,2.90 2dxd (13.78,10.48) (13.79,5.70)		6.82 (5) m		2.89 (1) 3.13-3.33 (3) 3.62-3.85 (4) all m		
32	1.90 "sextet"				3.03 (1) 3.17 (1) 3.23 (2) 3.36 (1) 3.57 (1) 3.76 (1) 3.89 (1) all m		0.72,0.81 2d (6.62)
33	1.98 (3) 2.36 (1) m			3.36 (4) 3.55 (2) 3.73-3.90 (2) 3.91-4.05 (2) all m			
34					3.02 (1) 3.30 (5) 3.78 (2) all m	1.21 d (7.03)	

Table 19: ^{1}H-NMR (300 MHz, acetone-d_6)

Ex	H-C(1)	H-C(3)	H-C(4)	H-C(6)	H-C(8)	H-C(7)	H-C(1')	H-C(2')	H-C(3')	H-C(4')/ H-C(N')
36	9.27 s	8.57 d (6.07)	8.37 d (6.10)	8.13,8.17 2d (7.37,8.27)		in the region 7.53-7.64 m	4.08 dxd (9.53,4.89)	2.75,2.90 2dxd (13.60,9.75) (13.60,4.80)		7.02 m
37	9.31 br s	8.69 d (6.14)	8.61 br d (6.07)	8.45 dxd (7.36,1.35)	8.22 br d (8.26)	7.69 dxd (8.15,7.45)	3.78 m	2.03 m		
38	9.43 br s	8.72 br d	8.69 d (6.16)	8.55 dxd (7.39,1.24)	8.43 br d (8.21)	7.85 dxd (8.15,7.47)	4.55 m	1.81,2.05-2.13, m		3.57,3.68 m
39	9.39 br s	8.70 br d	8.60 br d	8.47 d (7.34)	8.31 d (8.18)	7.74 br t	4.14 m			
41	9.43 br s	8.69 d (6.08)	8.58 d (6.15)	8.51 dxd (7.39,1.05)	8.39 d (8.22)	7.79 t (7.83)				
42	9.42 d (0.66)	8.67 d (6.10)	8.54 br d (6.07)	8.45 dxd (7.39,1.17)	8.39 d (8.22)	7.78 br t (7.82)				

Table 19 cont.:

Ex	H-C(5") H-C(6") H-C(7")	H-C(1")	H-C(2")	H-C(3") H-C(5")	H-C(4") H-C(6")	H-C(9") H-C(11")	H-C(8") H-C(12")	H-C(10")	NHCO-	$NHSO_2$-
36	6.89 m			7.38-7.47, 7.53-7.64 m				7.33 br t	10.23 s	
37			0.86,0.91 2d (6.72)	7.41-7.50 m		7.27-7.35,7.61 m			9.20 br s	
38				7.58-7.66 m		7.44 br t	7.58-7.66 m	7.33 br t	9.42 s	
39		1.30 d (7.05)		7.39-7.51 m		7.43 m	7.61 br d	7.33 br t	9.23 br s	7.55 br s
41				7.48 br d (8.64)	7.23 br d (8.66)	7.39 br t	7.52 br d (7.32)	7.29 br t		9.66 br s
42				7.15 m				7.00 br t [H-C(4")]		9.51 br s

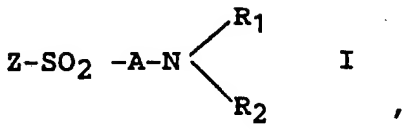
Table 20

ID	IC_{50} [1] (μM)
1	promotion [2]
2	promotion [3]
7	310
10	520
11	570
21	600
22	310
25	67
30	275
31	promotion [4]
35	263
37	470
38	130
40	435
41	promotion [5]
43	190

[1] Compounds are only listed if their IC_{50} is lower than 600μM.
[2] Promotion of the hydrolysis rate at 100mM: 138% of the value in absence of an inhibitor.
[3] Promotion of the hydrolysis rate at 100mM: 125% of the value in absence of an inhibitor.
[4] Inhibition at 100μM: 70.1%, at 300μM 54.0%.
[5] Inhibition at 10μM: 31.6%, at 100μM 28.3%.

CLAIMS

1. Aromatic sulfonamide derivatives of the formula



I ,

wherein

Z is phenyl, naphthyl, (5)- or (8)-isoquinolyl, possibly substituted by halogen

A is a single bond or an amino acid group where the N atom of the amino acid group is bound to SO_2 and its carboxyl group to the N atom of the above identified general formula

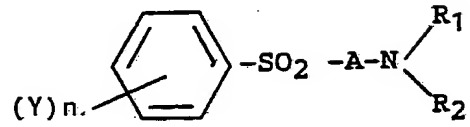
R_1 is hydrogen, and

R_2 is biphenyl, a C_2 to C_6 alkylene group; or is phenyl if Z is neither naphthyl nor chloronaphthyl, and A is not a single bond; or

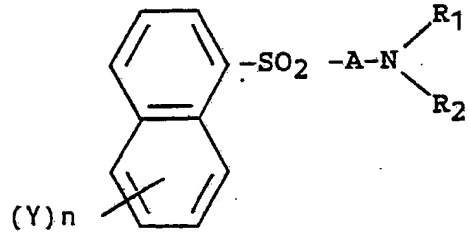
R_1 and R_2 together form the piperazine ring.

and its pharmaceutically acceptable non-toxic acid additional salts with inorganic or organic acids.

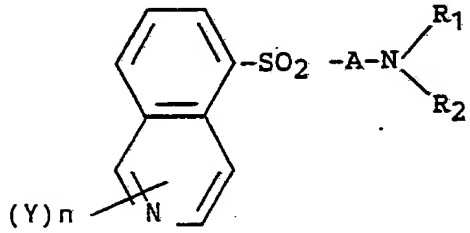
2. Derivatives of claims 1 having one of the formulas



II,



III, or



IV,

wherein

A, R_1 and R_2 have the meaning as defined in claim 1,

Y is F, Cl, Br, being the same or different, and

n is 0, 1 or 2.

3. Derivatives of claim 1 or 2, wherein A is the L-phenylalanine, L-alanine, L-proline, L-valine, L-tryptophane or L-tyrosine group.

4. Derivates of claim 1 or 2, wherein A is the L-phenylalanine, L-alanine, L-valine or L-proline group.

5. Derivates of claim 1 or 2, wherein A is the L-phenylalanine group.

6. Derivates of any of the preceding claims, wherein
R_1 is hydrogen,
R_2 is biphenyl.

7. Derivates of any of the claims 1 to 5, wherein R_1 and R_2 together form the piperazine ring.

8. Derivates of any of the claims 1 to 5, wherein
R_1 is hydrogen, and
R_2 is C_3 or C_6 alkylene.

9. Derivates of any of the claims 1 to 5, wherein
A is a single bond
R_1 is hydrogen, and
R_2 is biphenyl.

10. Derivates of any of claims 2 to 5 with formula III, wherein
Y is F or Cl in 5-position
n is 1
R_1 is hydrogen, and
R_2 is biphenyl.

11. Derivates of any of claims 2 to 5 with formula IV, wherein
Y is hydrogen
n is 0
R_1 is hydrogen, and
R_2 is biphenyl.

12. Use of the compounds of any of the preceding claims including the derivates of formula I, wherein A is a single bond, Z naphthyl or chloronaphthyl, R_1 hydrogen, and R_2 phenyl,
as inhibitors of Ca^{2+} - dependent enzymes and proteins.

13. Use according to claim 12 as inhibitors of Phospholipase A_2 and protein kinases.

14. A pharmaceutical composition for use as claimed in any of the claims 12 and 13 with pharmaceutically acceptable non-toxic addition salts including the salts of inorganic acids, namely hydrochloric acid, phosphoric acid and sulfuric acid; and the salts of organic acids namely citric acid, tartaric acid and methanesulfonic acid.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/01678

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 C 311/14, 311/15, 311/16, 311/21, C 07 D 217/22 295/182, 295/26, A 61 K 31/18, 31/47, 31/495

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	C 07 C; C 07 D; A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	Chemical Abstracts, volume 114, no. 24, 17 June 1991, (Columbus, Ohio, US), see page 392, abstract 234866m, & JP, A, 2273610 (Hair growth stimulants containing protein kinase-inhibiting sulfonamides) 8 November 1990 --	1-11, 14
X	STN International, File CA, STN accession no. CA 105(7):56886x, M Inagaki et al: "Naphthalenesulfonamides as calmodulin antagonists and protein kinase inhibitors", & Mol. Pharmacol., 29(6), 577-81, 1986 --	1-11, 14
X	STN International, File CA, STN accession no. CA 110(11):93380b, R J Juszozak et al.: "Inhibition of cytotoxic T lymphocyte-mediated lysis and cellular proliferation by isoquinoline sulfonamide protein kinase inhibitors. Evidence for the involvement of protein kinase C in lymphocyte function", & J. Biol. Chem., 264(2), 810-15, 1989 --	1-11, 14

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
24th April 1992	19. 05. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Natalie Weinberg

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	STN International, File CA, STN accession no. CA 110(25):227610n, T Chijiwa et al: "A newly synthesized selective casein kinase I inhibitor, N-(2-aminoethyl)-5-chloroisoquinoline-8-sulfonamide, and affinity purification of casein kinase I from bovine testis", & J. Biol. chem., 264(9), 4924-7, 1989	1-11, 14
X	Methods in Enzymology, vol. 102, 1983, R C Hart et al.: "Hormone Action, Part G, Calmodulin and Calcium-Binding Proteins. Synthesis and Characterization of Calmodulin Antagonistic Drugs ", pages 195-204, page 197	1-11, 14
X	Chemical Abstracts, volume 112, no. 25, 18 June 1990, (Columbus, Ohio, US), Tokumitsu, Hiroshi et al.: "KN-62, 1-(N,O-bis(5-isoquinolinesulfonyl)-N-methyl-L-tyrosyl)-4-phenylpiperazine, a specific inhibitor of calcium/calmodulin-dependent protein kinase II", see page 399, abstract 233042m, & J. Biol. Chem. 1990, 265(8), 4315-20	1-11, 14
X	Patent Abstracts of Japan, Vol 11, No 297, C448, abstract of JP 62- 87581, publ 1987-04-22 Hokuriku Seiyaku Co Ltd	1-1, 14
X	EP, A2, 0187371 (ASAHI KASEI KOGYO KABUSHIKI KAISHA ET AL.) 16 July 1986, see the claims; page 2 lines 1-10, pages 76,78,80	1-11, 14
X	EP, A1, 0061673 (ASAHI KASEI KOGYO KABUSHIKI KAISHA ET AL.) 6 October 1982, see claims 1,2,5,6; page 2, lines 1-5	1-11, 14

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	EP, A2, 0138720 (DROPIC SOCIÉTÉ CIVILE DE GESTION DE DROIT DE PROPRIÉTÉ INDUSTRIELLE CHOAY) 24 April 1985, see claims 1,18,19	1-11, 14
X	EP, A1, 0287696 (ASAHI KASEI KOGYO KABUSHIKI KAISHA) 26 October 1988, see page 3, lines 5-11; the claims	1-11, 14
X	DE, A, 2218787 (MERCK & CO. INC.,) 2 November 1972, see the claims	1-11, 14
X	EP, A2, 0333557 (ATOCHEM) 20 September 1989, see the claims	1-11

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 12, 13 because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the the claims. It is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additonal fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional seach fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/EP 91/01678

SA 50646

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 28/03/92 The European Patent office is in no way liable for theseparticulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A2- 0187371	16/07/86	JP-A-	61227581	09/10/86
		US-A-	4678783	07/07/87
		JP-A-	61152658	11/07/86
EP-A1- 0061673	06/10/82	JP-B-	1044188	26/09/89
		JP-C-	1557669	16/05/90
		JP-A-	58121278	19/07/83
		US-A-	4456757	26/06/84
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		US-A-	4560755	24/12/85
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		JP-B-	2027992	20/06/90
		JP-A-	58121279	19/07/83
		JP-C-	1499131	29/05/89
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		JP-C-	1508507	26/07/89
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		FR-A-B-	2553414	19/04/85
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		US-A-	4871843	03/10/89
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		NL-A-	7204774	23/10/72
		US-A-	3828078	06/08/74
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		JP-A-	2004766	09/01/90

For more details about this annex : see Official Journal of the European patent Office, No. 12/82

EPO FORM P0479

AN 1993:559909 ZCAPLUS

DN 119:159909

TI Aromatic sulfonamide derivative inhibitors of calcium-dependnet enzymes and phospholipase A_2

IN Dumont, Raymond

PA Pharno-Wedropharm G.m.b.H., Germany

SO PCT Int. Appl., 58 pp.
CODEN: PIXXD2

PI WO9305014 A1 930318

DS W: AT, AU, BB, BG, BR, CA, CH, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MW, NL, NO, PL, RO, SD, SE, SU, US
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG

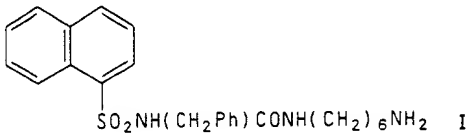
AI 91WO-EP01678 910905

DT Patent

LA English

OS MARPAT 119:159909

GI



$SO_2NH(CH_2Ph)CONH(CH_2)_6NH_2$ I

AB Arom. sulfonamides $ZSO_2ANR^1R^2$ [A = direct bond, amino acid residue with its N atom bound to the SO_2 moiety and the carboxyl group bound to the N-atom moiety; R^1 = H; R^2 = biphenyl, C_{2-6} alkylene, Ph (only if Z ≠ naphthyl or chloronaphthyl and A ≠ direct bond); R^1R^2 may form a piperazine ring], useful as inhibitors of phospholipase A_2 and calcium-dependent enzymes, and which may be of use in the treatment of inflammation, infarct, and arthritis (no data), are prepd. Thus, the HCl salt of sulfonamide I, prepd. from chloronaphthalenesulfonyl chloride, N-tert-BOC-L-phenylalanine, and N-BOC-6-aminohexane, exhibited 50% inhibition concn. of bovine pancreatic phospholipase A_2 at 67 μm.

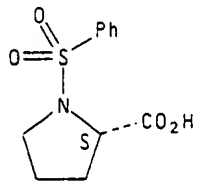
IT 88425-46-1
(condensation of, intermediates for calcium-dependent enzyme and phospholipase A_2 inhibitors from)

RN 88425-46-1 ZCAPLUS

CN L-Proline, 1-(phenylsulfonyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 88425-46-1 ZCAPLUS



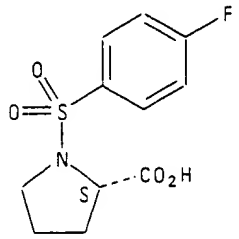
IT 97801-56-4P

(prepn. and reaction of, as intermediates of calcium-dependent enzyme and phosphokinase inhibitors)

RN 97801-56-4 ZCAPLUS

CN L-Proline, 1-[(4-fluorophenyl)sulfonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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